

REMARKS/ARGUMENTS

With this amendment, claims 53 and 55-74 are pending. Claim 59 is cancelled without prejudice to subsequent revival. For convenience, the Examiner's rejections are addressed in the order presented in a February 18, 2004 Office Action.

I. Status of the claims

Claim 53 is amended at step i) a) to recite that the cell comprises a heterologous accessory enzyme and a substrate of the heterologous accessory enzyme. Support for this amendment is found throughout the specification, *e.g.*, at page 26, lines 24-26 and at original claim 59. Claim 53 is also amended to recite a step of allowing formation of the nucleotide sugar and transfer of a sugar from the nucleotide sugar to the acceptor saccharide to form the product saccharide. Support for this amendment is found throughout the specification, for example, at page 17, lines 12-28; at page 46, lines 1-2; and at Examples 1-7, pages 59-64. These amendments add no new matter.

Claim 59 is cancelled without prejudice to subsequent revival. Claims 60 and 61 previously depended from cancelled claim 59 and have been amended to depend from claim 53. These amendments add no new matter.

New claim 73 depends from claim 53 and recites an additional step of detecting the product saccharide. Support for this amendment is found throughout the specification, for example, at page 61, lines 1-5. New claim 74 depends from claim 53 and recites an additional step of isolating the product saccharide. Support for this amendment is found throughout the specification, for example, at page 46, lines 6-20. These amendments add no new matter.

III. Objections to the drawings

On the Office Action Summary page, the Examiner objected to the drawings filed on November 17, 2004. No explanation of the objections was provided in the Office Action. In a telephone conversation with Applicant's representative Beth Kelly, the Examiner stated that a Notice of Draftperson's Drawing Review had been sent previously. Applicant's were unable to

find such a document in their files or evidence that such a review had been sent with any Office Action. However, a Notice of Draftperson's Drawing Review was sent in a related divisional application (USSN 09/757,289, filed January 8, 2001). In order to expedite prosecution and noting that nearly two years passed between the filing of the previous response and the mailing of the present Office Action, Applicants submit corrected drawings in response to the objections of the Notice of Draftperson's Drawing Review issued for the '289 application.

II. Rejections under 35 U.S.C. §112, first paragraph, written description

Claims 53 and 55-72 are rejected under 35 U.S.C. §112, first paragraph for allegedly failing to comply with the written description requirement. According to the Office Action, the specification lacks description of the claimed invention, "in such full, clear, concise, and exact terms" that a skilled artisan would recognize that Applicants had possession of the claimed invention at the time of filing. (Office Action at page 3.) To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

The basis of the rejection is that the specification allegedly provides adequate description of only one representative member of the claimed genus, *e.g.*, production of sialylactose using *E. coli* that express a CMP-sialic acid synthase/ α 2,3-sialyltransferase fusion protein. With regard to the CMP-sialic acid synthase/ α 2,3-sialyltransferase fusion protein the Office Action appears to assert that the sequence of the fusion protein is required to meet the description requirement. However, Applicants assert that the application does provide support for the full concept of the claimed genus, and moreover, the enzymes and oligosaccharides used in the claimed methods were well known at the time of filing and the descriptions provided easily meet the properly applied standard of written description.

The Office Action appears to assert that the inventors were not in possession of the claimed invention at the time of filing because not all species of the claimed genus were reduced to practice. However, under United States patent law, invention refers to the inventor's conception of an idea, rather than to a physical manifestation of the idea, *e.g.*, actual reduction to practice. The United States Supreme Court has stated that "[i]t is well settled that an invention may be patented before it is reduced to practice." *Pfaff v. Wells*, 48 USPQ2d 1641, 1644 (U.S.

Supreme Ct. 1998); *see also* MPEP 2163(II)(A)(2)(a). The applicant can demonstrate conception and satisfy the requirement for written description by describing the invention with "sufficient clearness and precision" to allow one of skill in the art to practice the invention as intended by the inventor. *Pfaff* at 1644. Reduction to practice is not required.

According to the Federal Circuit, Applicants have some flexibility in the "mode selected for compliance" with the written description requirement. *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886, 1896 (Fed. Cir. 2004). In *Rochester*, the Federal Circuit cited *In re Herschler*, where the CCPA found that "claims drawn to the use of known chemical compounds in a manner auxiliary to the invention must have a corresponding written description only so specific as to lead one having ordinary skill in the art to that class of compounds." *In re Herschler*, 200 USPQ 711, 718 (CCPA, 1979). Moreover, it is well settled that the description need only describe in detail that which is new or not conventional. *See Hybritech v. Monoclonal Antibodies*, 231 USPQ 81, 94 (Fed. Cir. 1986); M.P.E.P. 2163.

The concept of the claimed genus of methods is fully described in the specification, which includes recitation of a representative number of species for the accessory enzymes, glycosyltransferases, and product saccharides used in the claimed methods. The steps of the claimed methods are, *e.g.*, producing a product saccharide by contacting a microorganism or plant cell that comprises a heterologous accessory enzyme and a heterologous glycosyltransferase with an acceptor saccharide and allowing formation of the nucleotide sugar and transfer of a sugar from the nucleotide sugar to the acceptor saccharide to form the product saccharide. These steps do not appear to be at issue. Rather, the Office Action appears to focus on the description of the accessory enzymes, glycosyltransferases, and product saccharides used in the claimed methods.

Accessory enzymes, glycosyltransferases, and product saccharides are adequately described in the specification and the description enables those of skill in the art to use the claimed methods. Moreover, the specification provides representative numbers of each genus, *i.e.*, accessory enzymes, glycosyltransferases, and product saccharides, as required by *Regents of the University of California v. Eli Lilly* 43 USPQ2d 1398, 1406 (Fed. Cir. 1997) and MPEP2163. For example, the specification provides specific examples of at least 12 accessory enzymes for

forming a nucleotide sugar. Specification at pages 29-34. Table 1 at page 28, also provides nine examples of cycles for forming nucleotide sugars, including the enzymes required to regenerate a nucleotide triphosphate from a nucleotide. Using a single enzyme as an example, at page 32 of the specification, ten UDP-Gal pyrophosphorylase enzymes with accession numbers are disclosed. Six are from prokaryotic or viral organisms: *Lactobacillus*, *E. coli*, *B. subtilis*, *Neisseria*, *Haemophilus*, and *Streptomyces*. Four are from eukaryotes: Rat, bakers yeast, mouse, and human. Similar analysis is done for the other enzymes disclosed throughout 6 pages of the specification. Thus, by providing detailed information about the identity of multiple accessory enzymes in the specification combined with well-known characteristics of enzymatic pathways to synthesize nucleotide sugars, applicants have adequately described the concept of this genus as required by *Herschler*, *Hybritech*, and *Lilly*.

Glycosyltransferases are similarly well described in the specification. Eukaryotic glycosyltransferases are described from page 19, line 1 through page 21, line 15. Embodiments include fucosyltransferases, galactosyltransferases, sialyltransferases, glucosyltransferases, N-acetylgalactosaminyltransferases, and mannosyltransferases. References are cited for enzymes from many different organisms and some Accession Numbers are given. For example, galactosyltransferases are listed starting at page 19, line 25 through page 20, line 14. Twelve different galactosyltransferases are disclosed from human, bovine, murine, and porcine sources, as well as an enzyme from the yeast *Schizosaccharomyces pombe*. $\alpha(1,3)$, $\alpha(1,2)$, and $\alpha(1,4)$ galactosyltransferases are disclosed, as is a ceramide galactosyltransferase. Similar disclosure is made for the other eukaryotic glycosyltransferases.

A number of prokaryotic glycosyltransferases are also disclosed starting at page 21, line 16 through page 22, line 25. Prokaryotic glycosyltransferases include enzymes involved in synthesis of LOS. Disclosed prokaryotic enzymes include galactosyltransferases, glucosyltransferases, N-acetylglucosaminyltransferases, fucosyltransferases, and glycosyltransferases involved in the synthesis of structures containing lacto-N-neotetraose. The enzymes come from a variety of prokaryotic sources, including *E. coli*, *Salmonella typhimurium*, *Klebsiella pneumoniae*, *S. enterica*, *Yersinia enterocolitica*, *Mycobacterium leprosum*, *Pseudomonas aeruginosa*, *Neisseria gonorrhoeae*, and *N. meningitidis*. References are cited for

each enzyme disclosed and some accession numbers are given. Thus, the description of glycosyltransferases used in the claimed methods is sufficient to meet the written description requirement under *Hybritech*, *Herschler*, and *Lilly*.

Both accessory enzymes and glycosyltransferases are well known to those of skill in the art. In addition to the disclosure found in the specification, numerous reference materials are available that discuss accessory enzymes and glycosyltransferases, for example biochemical textbooks. See e.g. Lehninger, *Principles of Biochemistry* (1984); Stryer, *Biochemistry* (1995); Zubay, *Biochemistry* (1986). As discussed above, neither accessory enzyme, nor glycosyltransferases must be described in detail in the specification. *Hybritech*, 802 F.2d at 1384.

The Office action also appears to assert that the description of oligosaccharide products and glycolipids in the specification does not adequately describe the claimed invention. Applicants respectfully point out that, oligosaccharide and glycolipid products were known at the time of filing. Again, under the standard set forth in *Herschler* and reiterated in *University of Rochester*, the description of known chemical compounds need only be so specific as to lead one of skill to that class of compounds. In addition, known compounds are not required to be described in detail. *Hybritech*, 802 F.2d at 1384. The application provides adequate description of oligosaccharides, including structural information. For example, product oligosaccharides are described at Table 1, page 45; at page 48, lines 19-25; at page 49, line 1 through page 5, line 10 (including Table 2); at page 52, line 10 through page 53, line 28; and at page 54, line 25 through page 57, line 10 (including Table 3). Thus, the description of product oligosaccharides made using the claimed methods is sufficient to meet the written description requirement under *Hybritech*, *Herschler*, and *Lilly*.

The Office Action also suggests that the sequence of the CMP-sialic acid synthase/ α 2,3-sialyltransferase fusion protein is required for allowance of the claims. However, the concept of fusion proteins was known at the time of filing and is described in the specification at original claims 62-64; at page 37, lines 4-19; and at WO99/31224, page 37, lines 18-19, which is incorporated by reference at page 64, lines 12-13. Moreover, the structure of the CMP-sialic acid synthase/ α 2,3-sialyltransferase protein was well known to those of skill at the time of filing the application, and thus, the sequence of the fusion protein is not necessary for

allowance under US law. In addition to publication in a PCT application, *i.e.*, WO99/31224, the CMP-sialic acid synthase/ α 2,3-sialyltransferase fusion protein was described in a scientific journal before the earliest priority date of the present application, *i.e.*, Gilbert *et al.*, *Nature Biotech.* 16:769-772 (1998). Thus, additional description of this fusion protein is not required, and moreover, the description of fusion proteins used in the claimed methods is sufficient to meet the written description requirement under *Hybritech*, *Herschler*, and *Lilly*.

In view of the above amendments and remarks, withdrawal of the rejections under 35 U.S.C. §112, first paragraph, for alleged lack of written description is requested.

III. Rejections under 35 U.S.C. §112, first paragraph, enablement

Claims 53 and 55-72 are rejected under 35 U.S.C. §112, first paragraph because, allegedly, the specification does not enable the full scope of the claims. The Office Action asserts that the specification provides guidance only for use of a transformed *E. coli* that expresses a CMP-sialic acid synthase/ α 2,3-sialyltransferase fusion protein and appears to allege that the nucleic acid sequences of the fusion protein must be disclosed within the specification.

To the extent the rejection applies to the amended claims, Applicants respectfully traverse. The Examiner appears to have focused improperly on inoperative embodiments, leading to the conclusion that undue experimentation would be required to identify biologically active enzymes and their encoding nucleic acids of the claimed invention. However, the proper test of enablement is “whether one skilled in the art could make or use the claimed invention from the disclosure in the patent coupled with information known in the art without undue experimentation” (*see, e.g.*, MPEP §2164.01). In the present application, one of skill would know how to avoid inoperative embodiments and make oligosaccharides using the claimed methods, without undue experimentation (*see, In re Cook and Merigold*, 169 USPQ 299, 301 (C.C.P.A. 1971)). Moreover, the present application provides guidance in the form of assays and working examples for identification of product oligosaccharides.

Claims reading on inoperative embodiments are enabled if the skilled artisan understands how to avoid inoperative embodiments. As described by the court in *In re Cook and Merigold*, 169 USPQ 302:

Many patented claims read on vast numbers of inoperative embodiments in the trivial sense that they can and do omit 'factors which must be presumed to be within the level of ordinary skill in the art'....There is nothing wrong with this so long as it would be obvious to one of ordinary skill in the relevant art how to include those factors in such a manner as to make the embodiment operative rather than inoperative.

See, In re Cook and Merigold, 169 USPQ at 302 (quoting in part *In re Skrivan*, 166 USPQ 85, 88 (C.C.P.A. 1970)).

Factors such as the amount of guidance presented in the specification and the presence of working examples must be considered to determine whether undue experimentation is required to practice the claimed invention (*see, Ex Parte Förmán*, 230 USPQ 546 (Bd. Pat. App. & Int. 1985) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988)). As described in *Wands*, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed" (*see, Wands*, USPQ2d at 1404, quoting *In re Jackson*, 217 USPQ 804 (Bd. Pat. App. & Int. 1982)).

The Office Action alleges that undue experimentation is required to search for and screen for any product oligosaccharide or glycolipid, to search for and screen for any glycosyltransferase that can be made in a fusion protein, to search for and screen for any acceptor saccharide, to transform any microorganism or plant cell with an expression construct that encodes the glycosyltransferase, to determine whether a transformant can synthesize the desired oligosaccharide or glycolipid product, and to search for or screen for any glycosyltransferase fusion protein to make the desired product. As argued in detail below, each of these assertions is incorrect in that the specification as filed provides more than adequate guidance to allow one of skill to practice the invention.

Regarding the alleged requirement for a user to search for and screen for any product oligosaccharide or glycolipid, Applicants respectfully point out that the choice of product will depend on the needs of the user. In addition, the structure of oligosaccharides and glycolipids was known to those of skill at the time of filing and the specification identifies and

provides the structure of many product oligosaccharides and glycolipids. See, *e.g.*, Table 1, page 45; at page 48, lines 19-25; at page 49, line 1 through page 5, line 10 (including Table 2); at page 52, line 10 through page 53, line 28; and at page 54, line 25 through page 57, line 10 (including Table 3).

Once the user has selected a desired product oligosaccharide, the choice of acceptor saccharide and appropriate glycosyltransferase and accessory enzyme can easily be made by one of skill based on the specification. Acceptor saccharides are disclosed throughout the specification, for example, at page 3, lines 9-11; at page 4, line 10; at page 4, line 28 through page 5, line 1; at page 6, lines 15-16; at page 7, line 1; at page 44, lines 21-29; at page 50, lines 1-5; age 51, lines 26-29; and examples 1-9. Based on the added sugar residue and the desired linkage, one of skill could easily use the specification to select an appropriate glycosyltransferase to perform the addition of the sugar. Guidance for selection of an appropriate glycosyltransferase is found throughout the specification, for example at Table 1; at page 49, lines 9-17; at page 50, lines 2-5 and 13-16. Glycosyltransferases are disclosed throughout the specification, for example at page 16, line 19 through page 26, lines 15; similarly accessory enzymes are disclosed at page 26, lines 16 through page 36, line 20. Those of skill would be able to select an appropriate accessory enzyme based, *e.g.*, on the donor sugar selected for synthesis of a particular oligosaccharide and the desired linkage to the acceptor saccharide.

According to the Office Action, the specification is not enabling for the full scope of the claims because allegedly the likelihood of success in making a fusion protein that could be used in the claimed methods, other than the exemplified CMP-sialic acid synthase/ α 2,3-sialyltransferase fusion protein, is low. First, Applicants respectfully bring to the Examiner's attention, that the invention is not limited to fusion proteins and that appropriate combinations of unfused heterologous glycosyltransferases and accessory enzymes can be used in the claimed methods without being fusion. Second, as discussed above, synthesis of fusion proteins comprising glycosyltransferases and accessory enzymes was well known at the time of filing. For example, WO99/31224 discloses the successful production of two fusion proteins, *i.e.*, a CMP-sialic acid synthase/ α 2,3-sialyltransferase fusion protein and a UDP-glucose 4' epimerase/ β -1,4-galactosyltrasferase. Construction of an α galactosyltransferase/UDP-Glc/Gal

eipmerase has been reported as well. *See, e.g.,* Chen et al., *J. Biol. Chem.* 275:31594-31600 (2000). Thus, the likelihood of success in making a fusion protein comprising a glycosyltransferase and an accessory enzyme is not low as alleged in the Office Action, and, moreover, is demonstrably well within the capability of one of skill in the art.

According to the Office Action, undue experimentation would be required to identify a microorganism or plant cell that could be transformed with an expression construct(s) to express the heterologous glycosyltransferases and accessory enzymes. However, given the basic molecular biology and protein expression techniques known to those of skill, this objection is clearly misplaced. For example, the specification provides ample guidance for use of plant cells and microorganisms other than *E. coli* in the claimed methods, *e.g.*, exemplary plant cells and microorganisms are found at page 38, lines 1-20; exemplary plant promoters are found at page 38, line 21 through page 39, line 19; exemplary yeast promoters are disclosed at page 39, line 25 through page 40, line 5; promoters and methods for exemplary bacteria, including *E. coli*, *Streptomyces*, *Bacillus*, and gram negative bacteria are disclosed at page 39, lines 20-21; page 40, lines 6-19; and page 40 line 26 through page 42, line 7.

Finally, using the specification and techniques well known at the time of filing those of skill would have been able to determine whether the desired product has been made, and thus, to distinguish between operative and inoperative embodiments of the invention.

In view of the above amendments and remarks, withdrawal of the rejection is respectfully requested.

IV. Rejections under 35 U.S.C. §112, second paragraph

Claims 53 and 55-72 are rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that the Applicants regard as the invention. Allegedly clarification is required for steps including permeabilizing the cell, adding sugar substrates, allowing the reaction to take place, and detecting/determining the presence of the oligosaccharide product.

To the extent the rejection applies to the amended claims, Applicants traverse. Applicants assert that one of ordinary skill in the art would understand the claimed invention in

light of the specification. "[35 U.S.C.] §112, second paragraph, requires a determination of whether those skilled in the art would understand what is claimed in light of the specification." *Orthokinetics v. Safety Travel Chairs Inc.*, 1 USPQ2d 1081 (Fed. Cir. 1986).

Claim 53 is now amended to recite a step of "allowing formation of the nucleotide sugar and transfer of a sugar from the nucleotide sugar to the acceptor saccharide to form the product saccharide." The remaining steps that allegedly lack clarification are, as one of skill would recognize, optional and are properly included as dependent claims. Thus, dependent claim 57 recites permeabilizing a cell and dependent claim 58 recites using an intact cell. Detection/determination of the product is also optional and is recited in new dependent claim 73.

The Office Action also alleges that claim 55 lacks antecedent basis, requires an endogenous glycosyltransferase, and does not further limit claim 53, from which it depends. Claim 55 is now amended to reiterate that the glycosyltransferase is a heterologous protein. At least in part, the rejection appears to be based on confusion regarding the definition of the term heterologous. A definition of heterologous protein is found at page 10, lines 18-25. According to the specification, a heterologous glycosyltransferases gene includes a gene endogenous to the host cell, that has been modified, *e.g.*, by being linked to a promoter or by being mutagenized. Claim 55 is appropriately directed to a heterologous glycosyltransferase that is encoded by a gene that occurs naturally in the host cell, but has been modified to increase its expression. Thus, claim 55 requires a heterologous glycosyltransferase and does not lack antecedent basis.

In view of the above amendments and remarks, withdrawal of the rejection is respectfully requested.

V. Rejections under 35 U.S.C. §102(b)

Claims 53, 56, 57, 58, and 72 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Samain *et al. Carbo. Res.* 320:35-42 (1997). To the extent the rejection applies to the amended claim, Applicants respectfully traverse the rejection.

To anticipate a claim, the reference must teach every element of the claim. "A claim is anticipated only if each and every element as set forth in the claim is found...in a single prior art reference." *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631, 2 USPQ2d

1051, 1053 (Fed. Cir. 1987). Thus, in order to anticipate, the cited references must contain every element of the claims at issue. The reference cited by the Office Action do not.

The claims are directed to methods of producing a product saccharide, by contacting a microorganism or plant cell that comprises a heterologous accessory enzyme for forming nucleotide sugar and a heterologous glycosyltransferase with an acceptor saccharide. The glycosyltransferase catalyzes transfer of a sugar from the nucleotide sugar to the acceptor saccharide to produce the product saccharide.

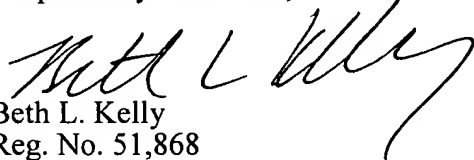
Samain *et al.* discloses an *E. coli* cell that expresses a NodC gene product, *i.e.*, a chitin oligosaccharide synthase protein. However, the reference does not disclose or suggest expression of a heterologous accessory enzyme in the same cell. Therefore, Samain *et al.* cannot not disclose all the elements of the claimed invention. Applicants respectfully request withdrawal of the rejection in view of the above amendments and remarks.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,


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Figure 1A

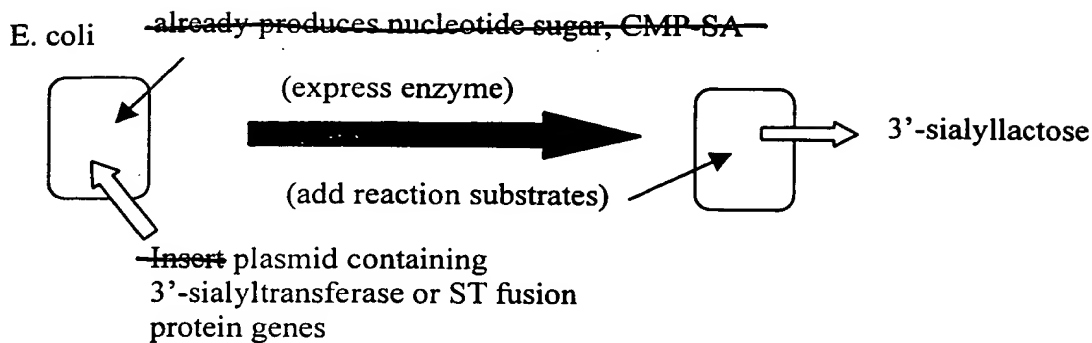


Figure 1B

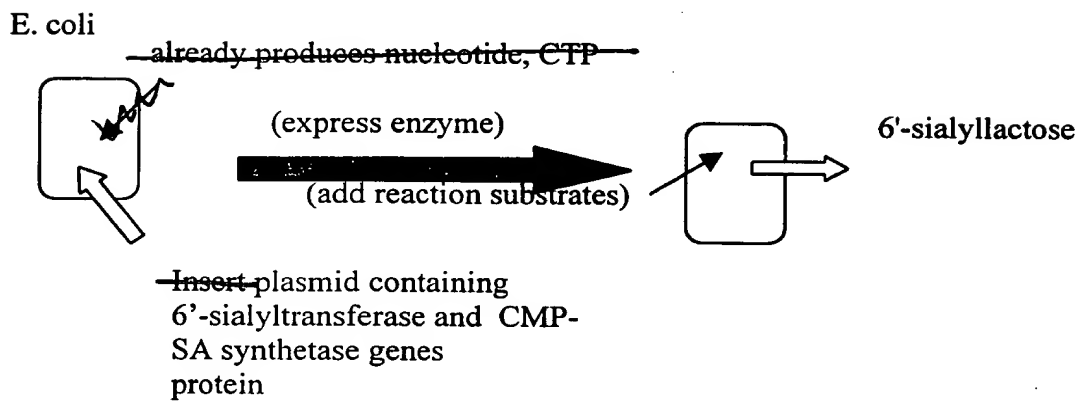
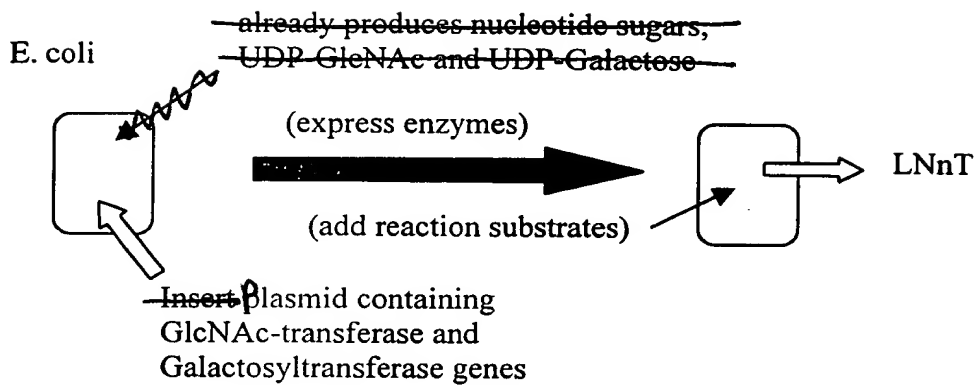




Figure 2



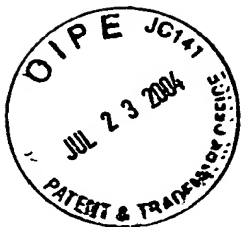
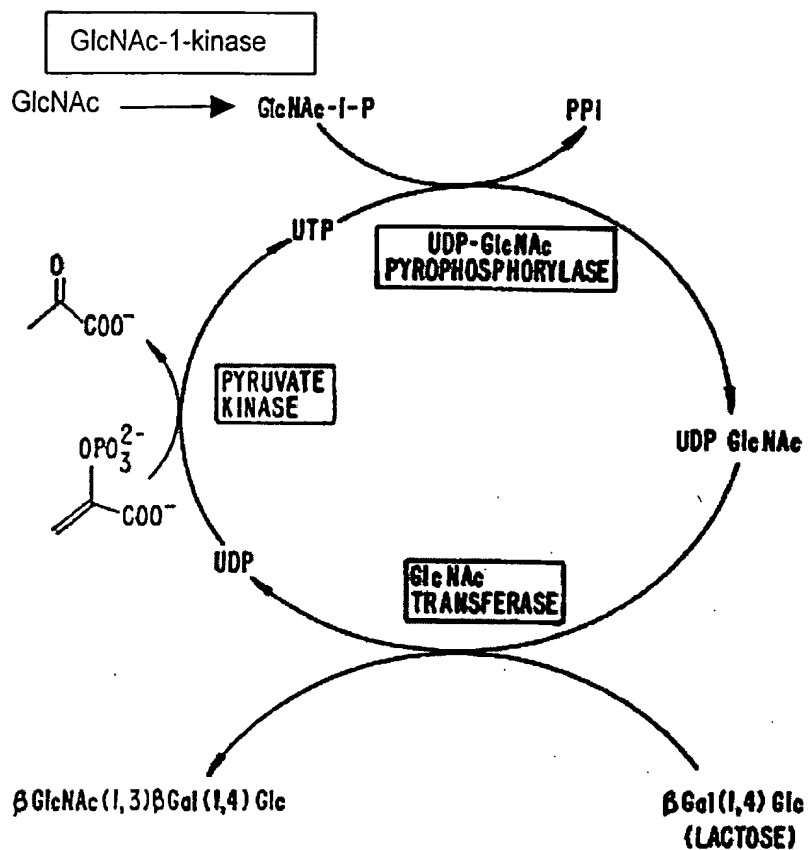


Figure 3



No Changes
Enlarged

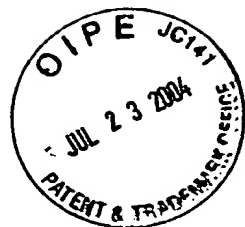


Figure 4A

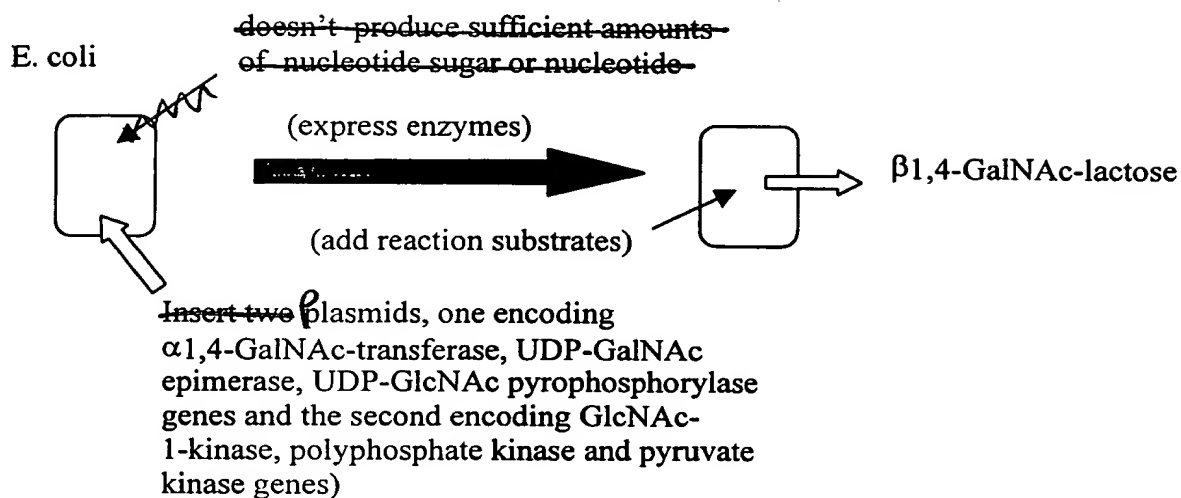


Figure 4B

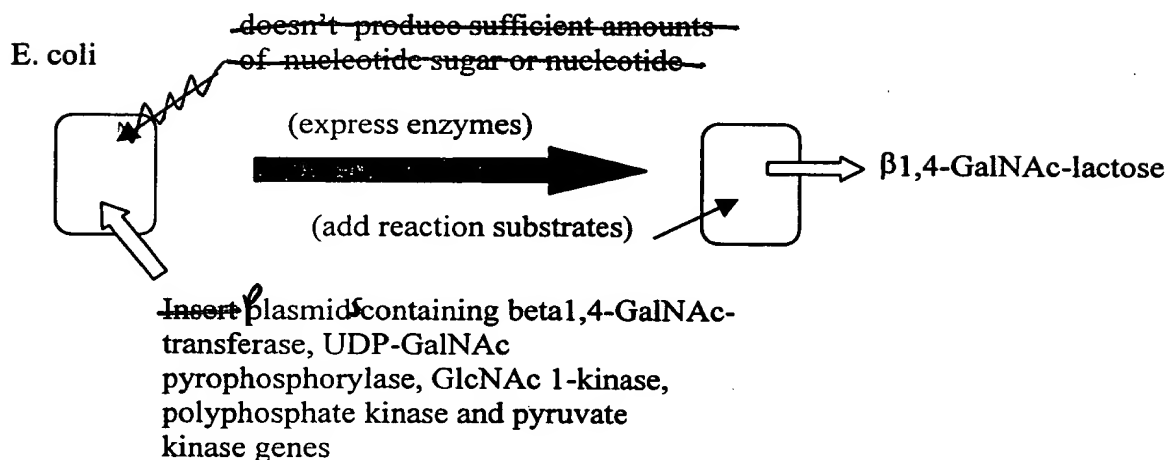




Figure 5A

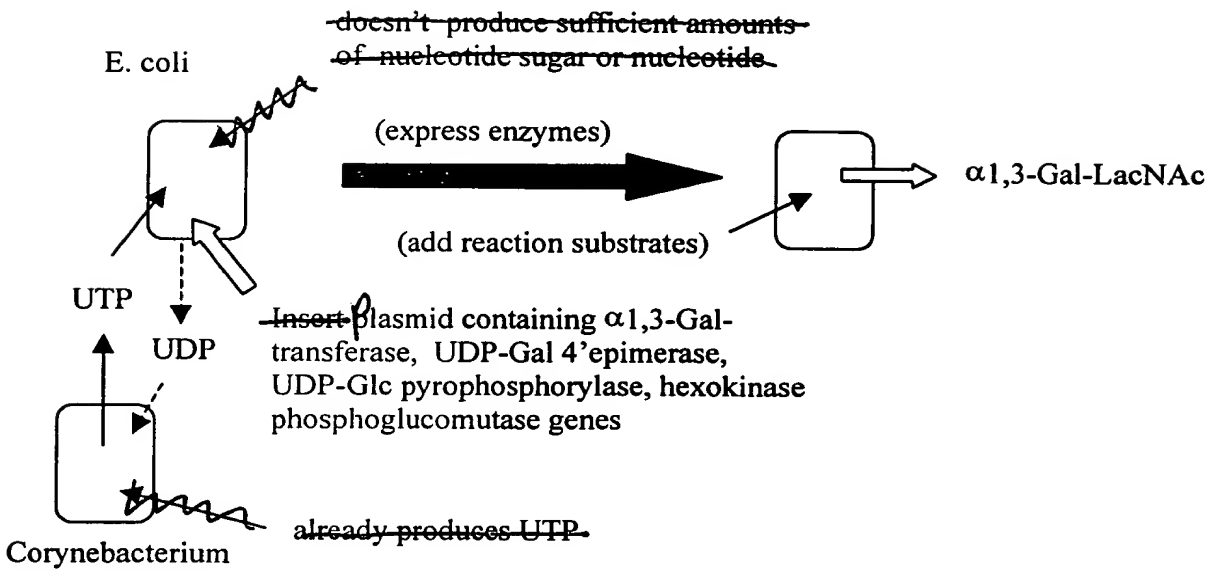
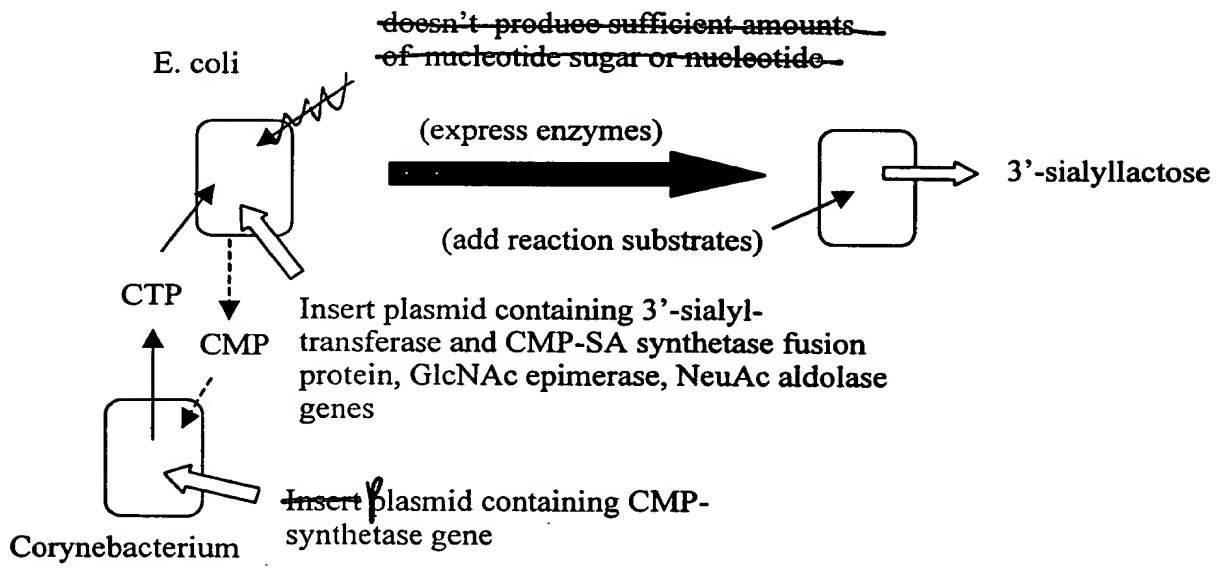


Figure 5B



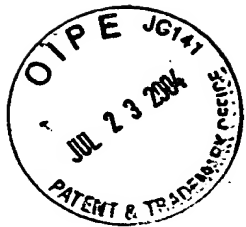
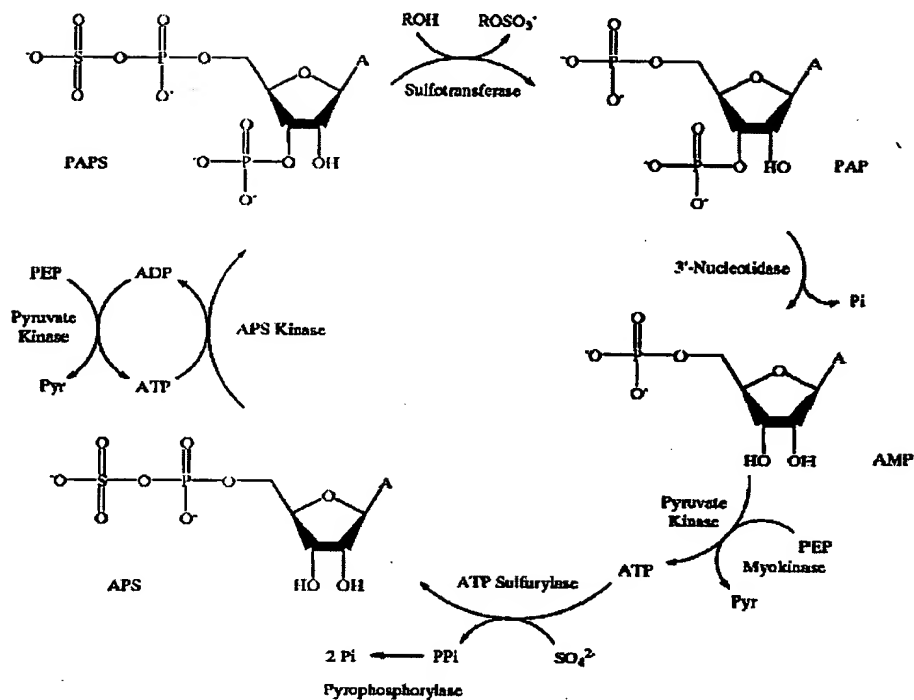


Figure 6



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 No changes

Figure 7A

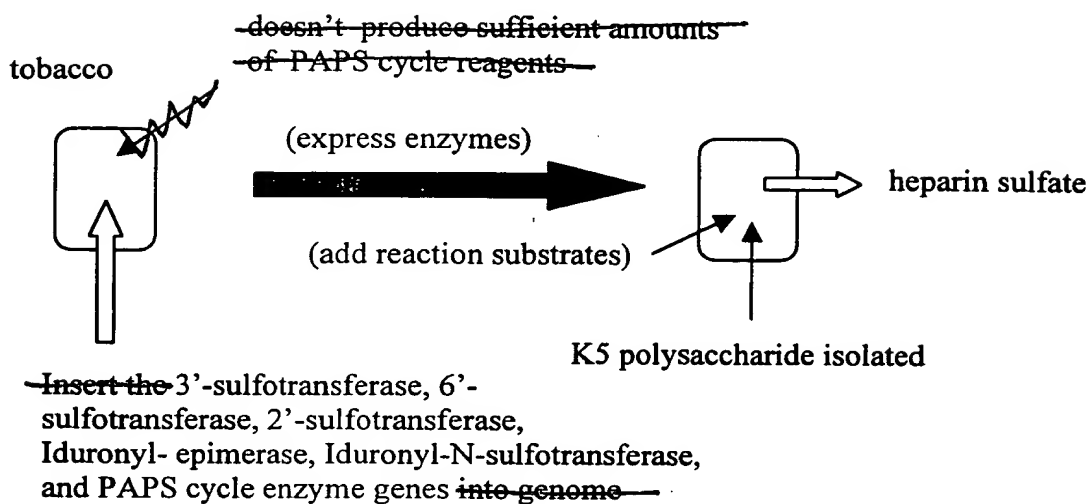


Figure 7B

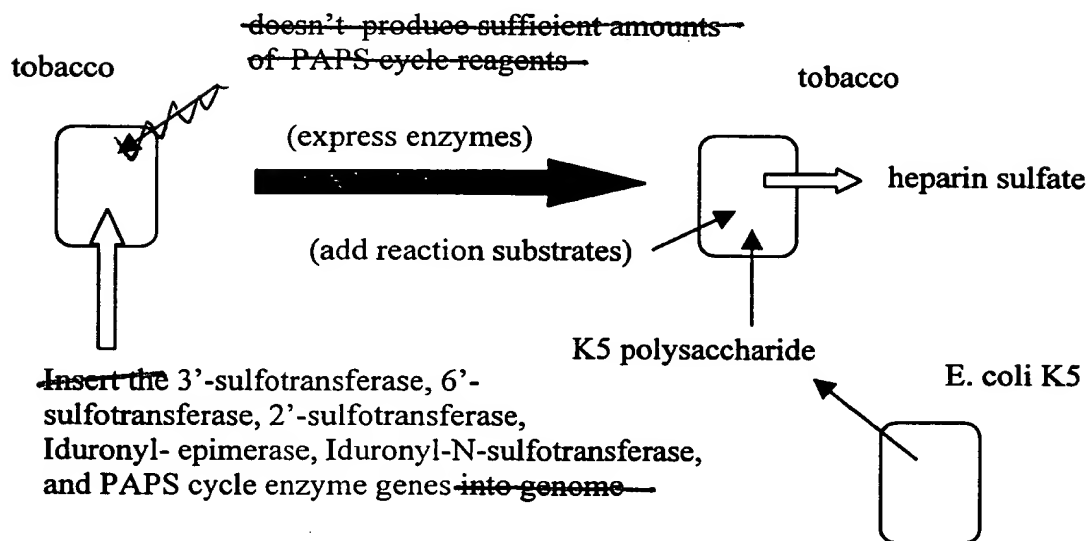
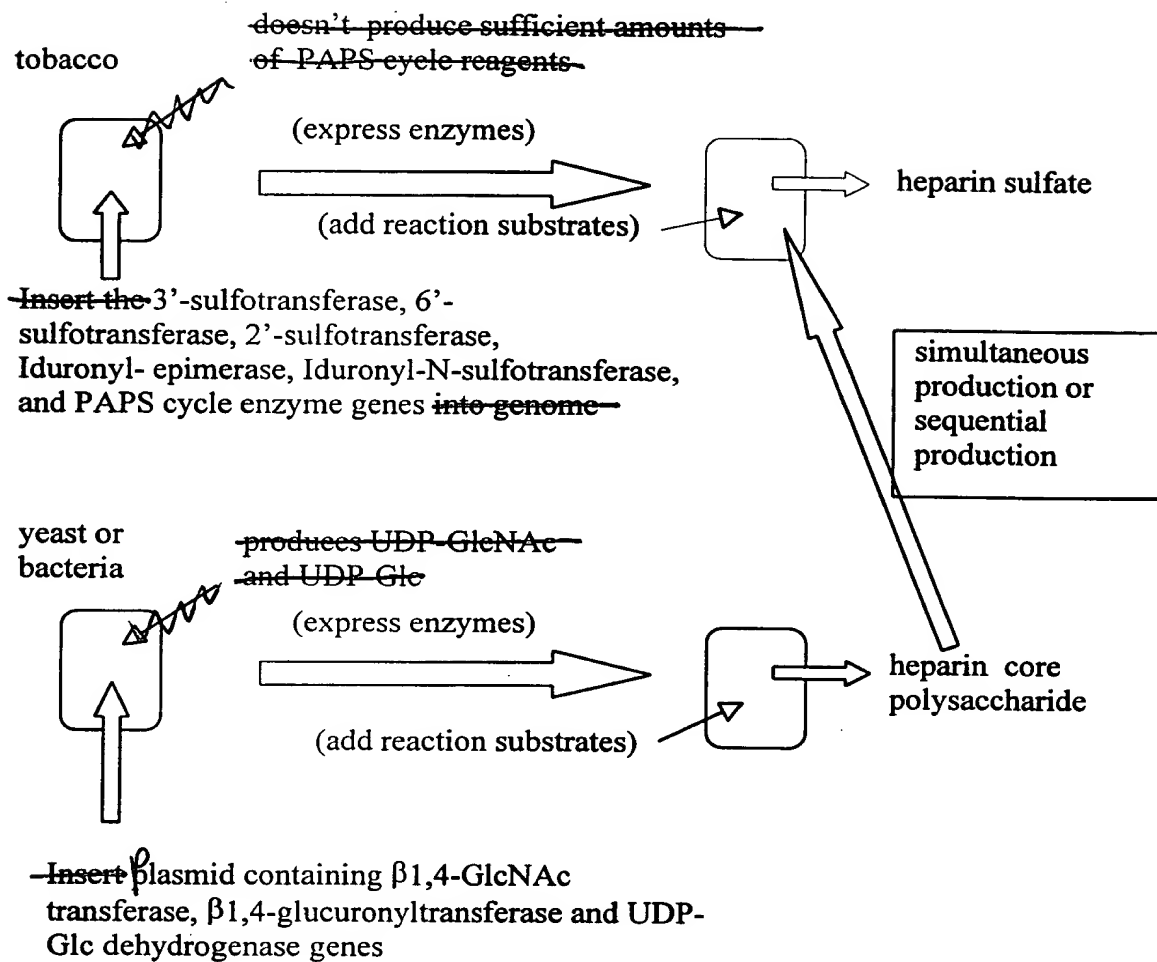




Figure 7C



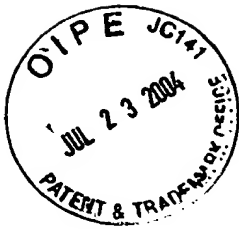
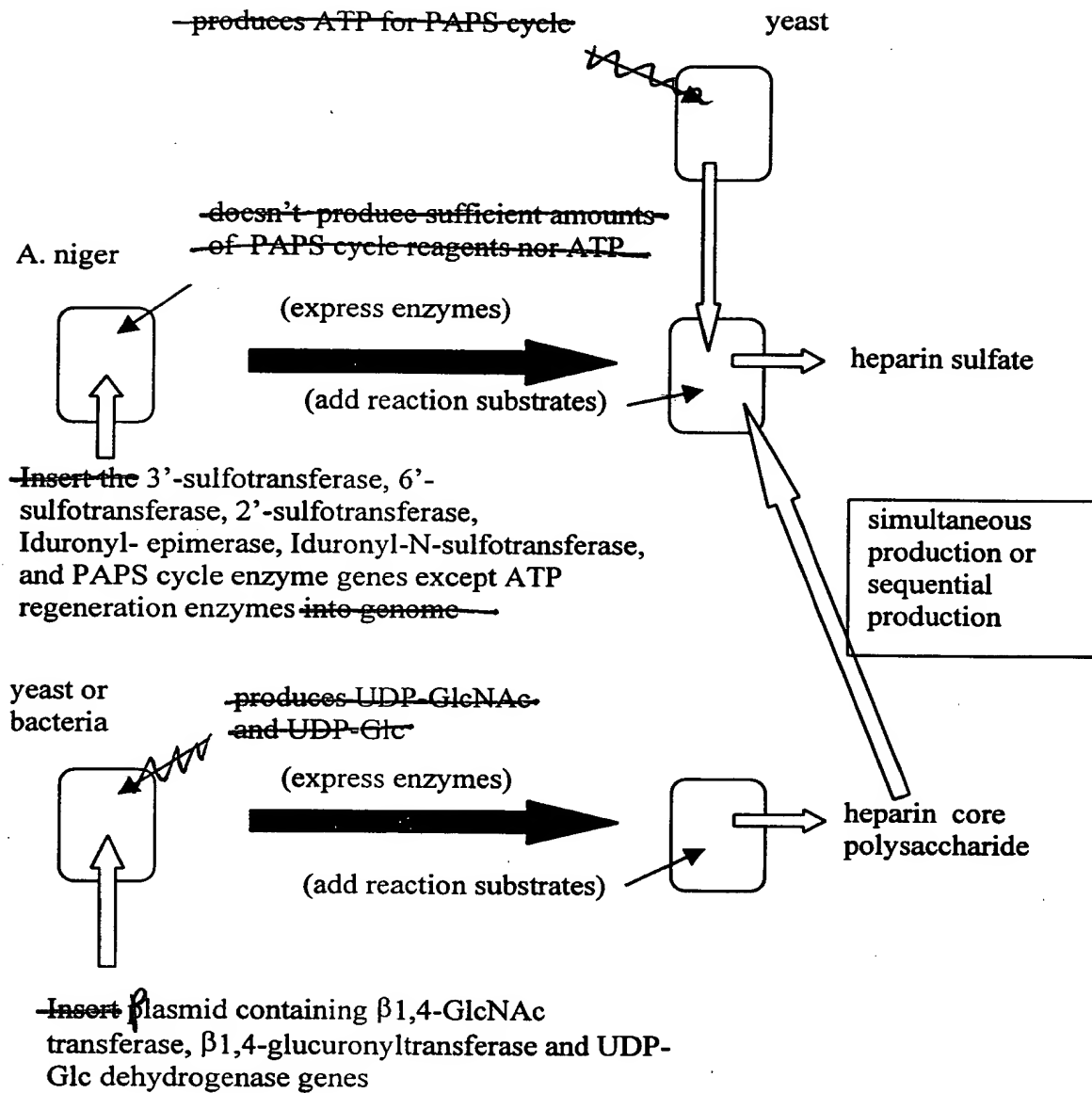


Figure 7D



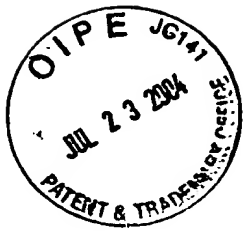
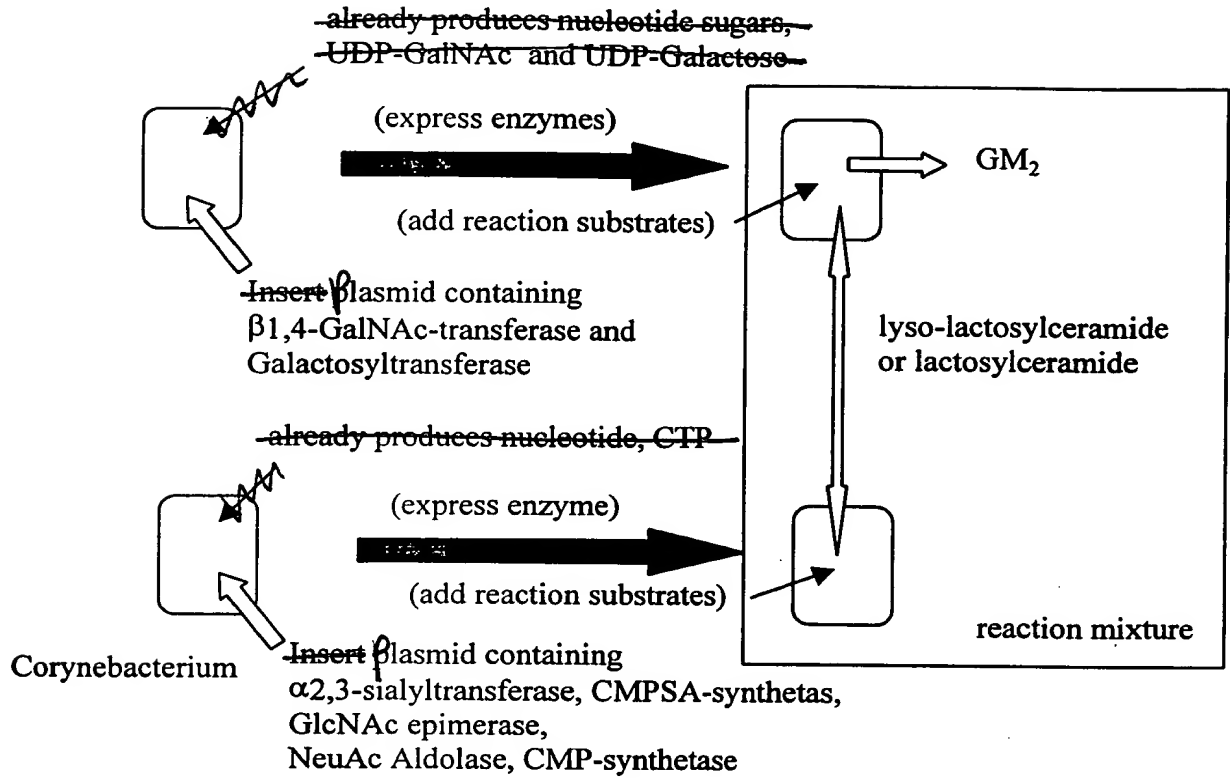


Figure 8



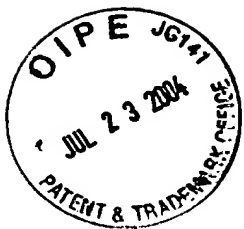
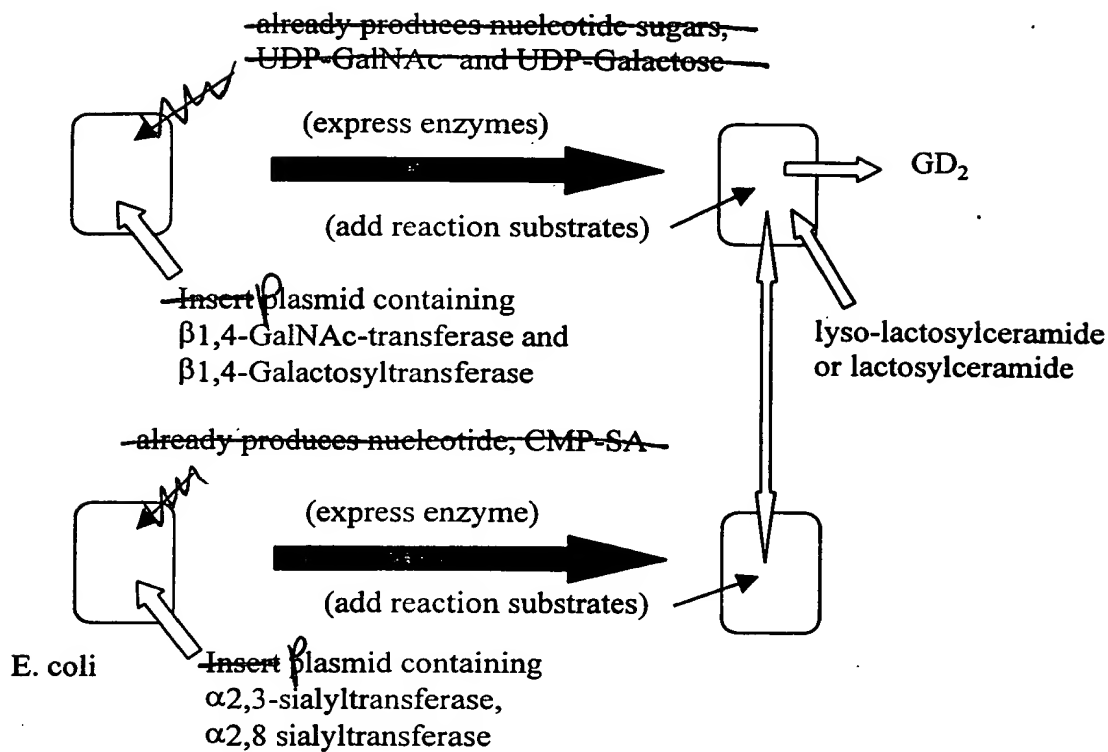


Figure 9



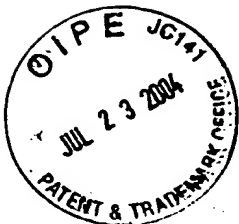


Figure 10

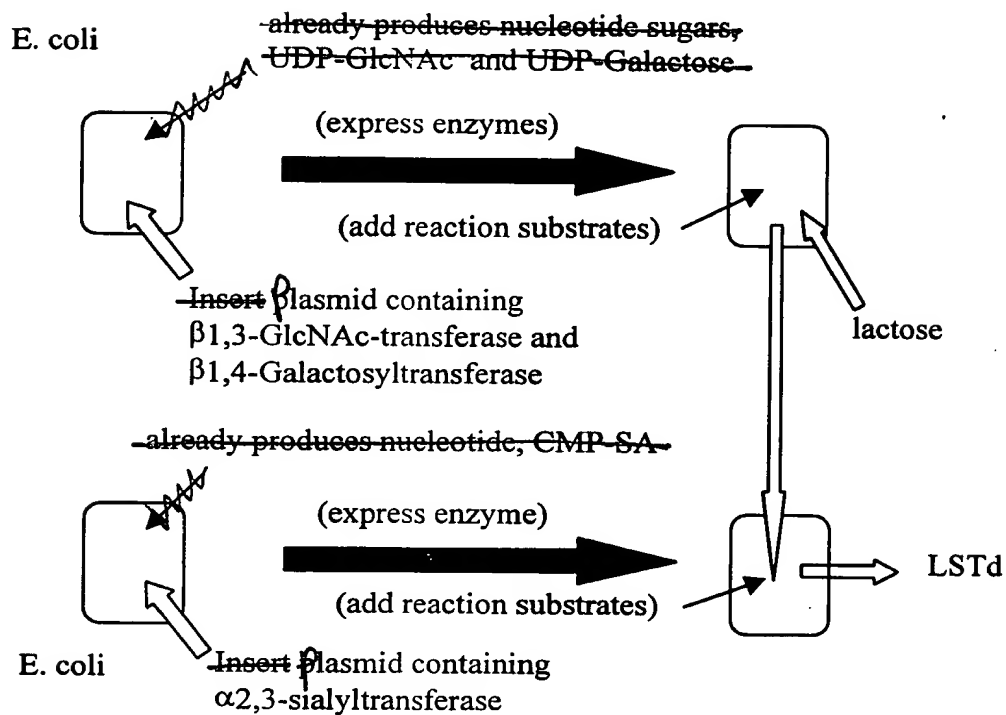




Figure 11A

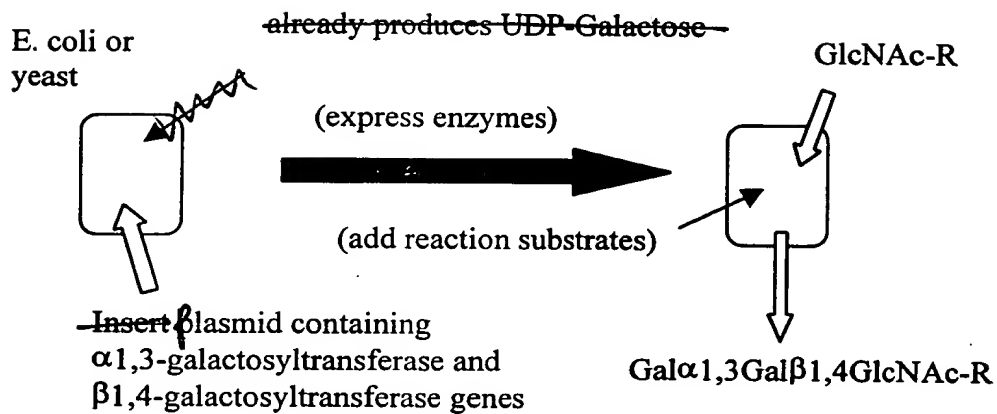


Figure 11B

